ASPECTS OF EPILEPTIC SEIZURES IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1

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ABSTRACT

Objectives. Neurofibromatosis type 1 (NF1) is a multisystem genetic neurocutaneous disease, with an autosomal dominant inheritance, affecting in a various degree the skin, the bones and also the nervous system. The neurological manifestation of this condition are due to peripheral nerves and also to associated brain lesions. Epilepsy can be one of the symptoms within NF1, with a double prevalence compared to the general population. The connection between seizures and neurofibromatosis type 1 is a clinically observable reality.

Methods. This paper is a retrospective observational study over a period of 4 years of children admitted to pediatric neurology clinic with a diagnosis of NF1. Clinical (neurological symptoms, such as seizures, their onset, psychiatric and cognitive profile) and laboratory data (routine electroencephalography, brain imaging exams) were analyze in order to find a cause-efect relation of this association and also the evolution predictive factors.

Results. There were evaluated 67 children with a diagnose of NF1 according to existing diagnostic criteria (1), and the association between epilepsy and neurofibromatosis type 1 has been reported in 4 patients, 2 boys and 2 girls. The onset of seizures had an average age of 36 months. 2 patients had drug resistant focal seizures associated with moderate and severe mental retardation. Cerebral magnetic resonance imaging (MRI), showed typical hiperintense lesions for this neurocutaneous syndrome only in 50% of cases.

Conclusions. The article will present clinical and laboratory correlations between the association of seizures and neurofibromatosis in these 4 children, with reference to data published in the literature in this area.

Key words: seizures, neurofibromatosis type 1, brain damage

INTRODUCTION

Neurofibromatosis type 1 (NF1) is a neurocutaneous disorder with an autosomal dominant pattern of inheritance, high penetrance and an incidence of 1/2500-3000. The gene responsible for this disease has been identified on chromosome 17 q11.2 and encodes the synthesis of a cytoplasmic protein called neurofibromin with a proto-oncogenes regulating role, resulting in tumor suppression. In up to 50% of cases the disease results from new mutations in the NF1 gene (2).

Clinically, the disease manifestations are highly variable, even within the same family, different persons being affected in various degrees of severity. The child with NF1 may have cutaneous, neurological, ocular, skeletal, endocrine and visceral signs. Cutaneous signs are the most easily identified only by inspection (undress the child!): hyperpigmented spots „cofee and milk" like coloured that are usually present at birth, measuring between 0.5 to 5 cm and with a macular shape, are found on the skin of the trunk or limbs, but not on the scalp, plants and palms. They grow in number and size in the first few months until the age of 2 years, but their number and size correlate with disease severity. It should be noted that a proportion of up to 25% of the population presents 1-4 hyperpigmented spots without any clinical significance (Figure 1). In order to be a positive diagnostic criterion of NF1, the number of spots a child should have must be at least 6, with a diameter over 0.5 cm in prepubertal individuals or over 1.5 cm in greatest diameter in postpubertal individuals (3).

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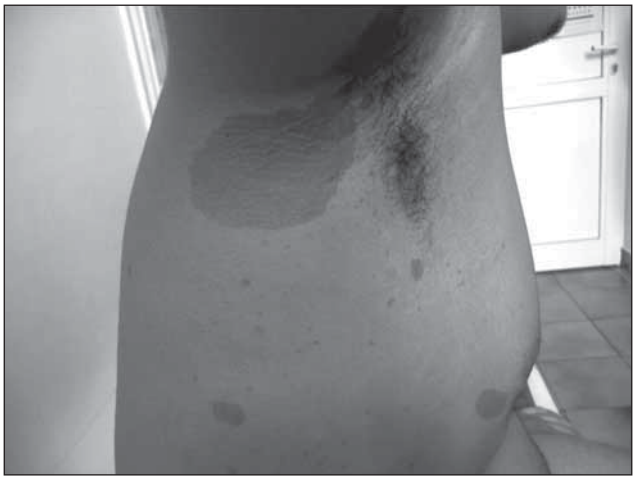

***FIGURE 1**. Hiperpigmentated spots and axillary freckles*

Among other hallmark lesions of the skin, NF1 includes axillary or inguinal freckles, which may occur also in the trunk, inframammary, or in the neck area. They are small hyperpigmented macules, with a diameter of 1-3 mm. The freckles are present in three quarters of NF1 cases and occur between age of 3-5 years, being a positive diagnostic criterion (Figure 1).

Along with the hyperpigmented macules on the skin, the children with NF1 may show neurofibromas, skin tumors, which are those that have given the name of disease (4). These occur in prepubertal age on the trunk, and grow in number and size at puberty and during pregnancy. They do not become malignant and may rarely be associated with pain or pruritus, most of the time posing only esthetic issues. 25% of cases of NF1 have plexiform neurofibromas, which grow along the peripheral nerves and are either congenital or occurring early in the first years of life and may be associated with pain or motor deficits. These skin tumors can become in time malignant. As positive diagnostic criteria for NF1 is considered the existence of at least two neurofibromas or one plexiform neurofibroma.

Neurological signs associated with NF1 are extensively variable. They can be „benign" – like macrocrania (occurs in 50% of cases and can be secondary to megalencephay or to obstructive hydrocephalus due to Sylvius aqueduct stenosis) or migraine-like headache. Also, it can be associated different brain tumors (different gliomas, the most commonly affecting the optic nerve, the optic pathway glioma being another positive diagnostic criterion, but also the brain stem and the cerebellum, and meningiomas). Besides these, children with NF1 can associate neurocognitive impairment (5) or seizures which may or may not be directly related to brain structural damage (6).

Bony manifestations include thoracic scoliosis, sphenoid wing and long bones dysplasia, tibial pseudoarthrosis or others. An obvious bone lesion is considered a positive diagnostic criterion for NF1.

The most common ocular manifestations are a form of asymptomatic iris neurofibromas, called Lisch nodules that develops between age of 5-10 years and represent a pathognomonic diagnostic criteria seen in adults or retinal fakomas.

The positive diagnostic of NF1 is made on a clinical basis and requires the presence of at least 2 diagnostic criteria. Besides the clinical characteristics described above, another diagnostic criteria (the 7th) is a positive family history for this disease.

OBJECTIVES AND METHODS

The medical files of children admitted with a diagnostic of NF1 to Pediatric Neurology Department over a period of four years, between February 2007 and February 2011, were analyzed. All these children had at least 2 diagnostic criteria for NF. The clinical data described in the medical files were evaluated by the authors to confirm the diagnosis of NF1 and to check the neurological complications. Children who associated epileptic seizures were included into the study.

The investigations performed by these children were processed by qualified medical personnel – the electroencephalography (EEG) by pediatric neurologists with EEG competence and the brain imaging by specialized radiologists.

The clinical data and the test results of the children with NF1 and associated seizures were analyzed, with emphasis on the onset, type of seizures and evolution of epilepsy, together with the related evaluations. It has been tried to find a cause-effect correlation between specific NF1 lesions and seizures, giving a special attention to brain imaging evaluation.

RESULTS

67 children with a diagnosis of NF1 were evaluated, only 4 of them associating seizures.

Valentin is a boy aged 6, with normal psychomotor development that was first hospitalized at age of 3 years for an afebrile, apparently primary generalized seizure, tonic-clonic type, without an apparent cause. The clinical evaluation showed 10 hyperpigmented maculae with a diameter over 0.5 cm and axillary freckles, so clinical diagnosis of

NF1 was positive. Neurological examination was normal, but with a cognitive level at a lower limit, noting as important the fact that he is brought up by his mother, also with a mild mental retardation, but no other clinical signs. His brother presents also staturo-ponderal hypotrophy and a mild cognitive deficit, but without any hyperpigmented spots.

At initial admission, the investigations performed, as standard serum tests and the awake EEG, which were normal. Brain scan showed an asymmetry of optic nerves without contrast enhancing, but without any abnormalities at eye examination. At that time, it was decided not to introduce continuous prophylactic antiepileptic treatment and to clinically follow-up the child.

Almost two months later, Valentin was admitted again because he repeated a seizure, this time was described as left hemibody focal motor type, with secondary generalization, lasting 10 minutes and followed by postictal hemiparesis. Repeated standard awake EEG showed focal epileptiform discharges, sharp waves elements, in the right frontal derivations. Cerebral magnetic resonance imagery (MRI) showed no changes in the brain parenchyma but persistent asymmetry of optic nerves, the right being enlarged, without gadolinium enhancement, arising the suspicion of an optic glioma. The introduction of carbamazepine as antiepileptic treatment was decided, with favorable evolution and still without seizure recurrence 3 years after the therapy was initiated.

Alexandru is a 15 year old boy with diagnosis of NF1 (13 cafe-au-lait spots with a diameter of 3-7 cm, axillary and inguinal freckles), known with epileptic seizures from the age of 11 years. The neurologic clinical examination showed microcephaly (<-2 standard deviation), bipyramidal asymmetrical syndrome, left < right, within a motor deficit as spastic tetraparesis and severe cognitive impairment (mental age below 3 years). Seizures were focal motor, involving the right hemi-body, with upper limb clonic movements and sometimes secondary generalization, with a variable frequency of 1 episode every couple of days or months.

As mentioned in his files, he was born from a normal pregnancy, with no significant family history and perinatal events, but at the age of 1 month and 2 weeks he had suffered an acute encephalitis due to a septicemia with unidentified germ, Alexandru being comatous and with associated multiorgan failure. After this severe infectious episode, the child presented a global developmental delay, with abnormal spastic gait acquisition at age 5.

Of conducted investigations in this patient, the EEG showed both focal lesional changes and epileptiform discharges in the left anterior derivations and the brain MRI indicated bilateral gliotic periventricular lesions, left > right, on the left parieto-occipital side also on the cortical level, associated with T2-hyperintense areas in the bilateral basal ganglia described with an acronym given by *neurofibromatosis bright objects* – NBO's.

Alexandru tried seven antiepileptic drugs in monotherapy or combination of 2-3, without complete control of seizures, his epilepsy being considered highly pharmaco-resistant, diagnosed as focal symptomatic epilepsy due to brain lesion related to encephalitic lesion, probably on a genetic predisposition related to NF1.

Iulia is a 14-year-old girl, known in the department of pediatric neurology from the age of one year for focal seizures, initially left and then right alternating seizures, then also primary generalized seizures of axial tonic type and myoclonic, with unfavorable evolution in time, at present still occuring 1-4 seizures/day or each several days. Polymorphic appearance of seizures along with specific EEG features – slow spike-waves complexes < 3 Hz were arguments for the diagnosis of Lennox-Gastaut syndrome (Figure 2).

Iulia's clinical examination revealed 13 hyperpigmented maculas > 1.5 cm and axillary and inguinal freckles, and her mother also has neurofibromatosis, three criteria for NF1 being thus found. The neurological examination did not show any motor deficits, but a severe cognitive impairment.

Brain imaging investigations, namely the brain MRI showed T2 hyperintense lesions bilateral in the in thalamus and also frontal cortical left> right, suggestive for NBO's (Figure 3).

Eight antiepileptic drugs were tried in mono- and polytherapy, but without any improvement as mentioned.

Because the imagistic exam didn't show any structural epileptogenic anomaly, her etiologic diagnosis was probably genetic, probably related to NF1.

Maria is a one year old girl, whose father was diagnosed with NF1 and who was admitted for one episode of complex febrile seizure involving right hemibody complex febrile (occuring at high temperature). Clinical examination revealed seven cafe-au-lait spots > 0.5 cm, and the neurological exam was normal. Her family history was negative for febrile convulsions or epilepsy.

The investigations – routine blood tests, EEG, brain imaging (MRI) – they were all normal. In

FIGURE 2. *EEG – generalized epileptiform discharges – slow spike-waves 2 Hz*

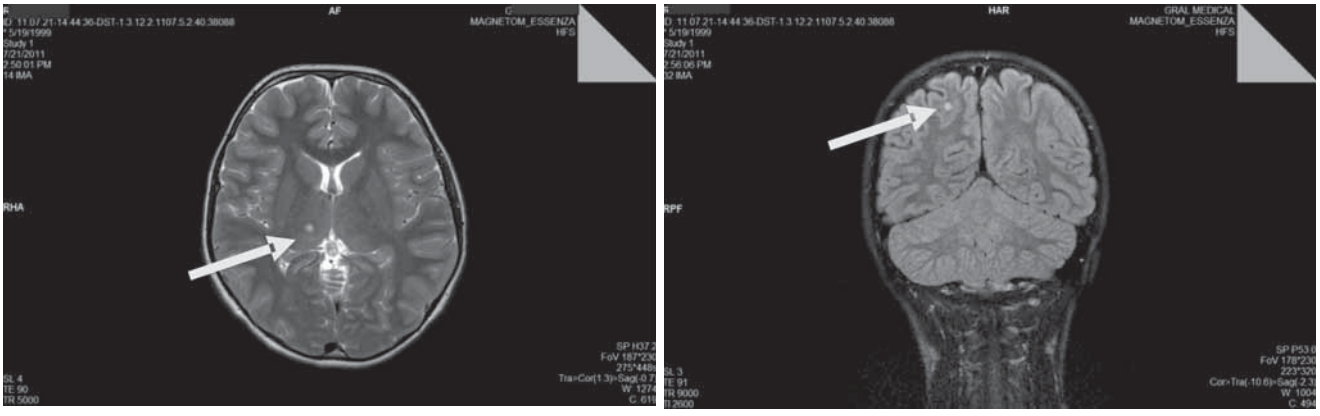

FIGURE 3. *(NBO's – thalamus and right frontal)*

Maria'case it was decided only to closely monitoring the child and after one year of follow-up after the diagnostic she hasn't repeated any seizure, but because of the focal aspect of febrile seizure, it was considered a complex febrile convulsion, probably related also to the genetic disease that she has, NF1.

DISCUSSIONS

Neurofibromatosis type 1 is a neurocutaneous syndrome characterized by peripheral signs such as café-au-lait spots, neurofibromas, Lisch nodules (corneal hyperpigmented areas) or axillary freckles, which associate central signs as optic nerve

glioma or type dysplastic bone lesions in a child whith first degree relatives with the same clinical signs. Seizures association was observed with a frequency twice higher than the general population, respectively 4-6% of patients with NF1 (3,7), in our study the rate being similar to that reported in the literature, namely 5% (4 patients out of 67 with a diagnostic of NF1 associated seizures). This association is not fully debated in the literature, so far only 5 published studies could be found when reviewing medical web-research engines.

These published studies have shown that the onset of seizures varies between the age of 4 days and 20 years, so it was not considered that NF1 may be associated with a specific epileptic syndrome at a certain age. In our study children had seizure onset at an age varying from 1-11 years (Table 1).

TABLE 1. *M – masculine, F – feminine, CPS – complex partial seizures, SPS – simple partial seizures, LGS – Lennox-Gastaut syndrome, CFS – complex febrile seizures; ☺ – favorable; ☻ – unfavorable*

Name	Gender	Epileptic seizures onset (years)	Seizures type	Cerebral MRI	Evolution
Valentin	M	3	CPS	-	☺
Alexandru	M	11	SPS	Gliosis + NBO's	☻
Iulia	F	1	Focal, myoclonic, tonic (LGS)	NBO's	☻ ☻
Maria	F	1	CFS	–	☺

Age of children is important for determining seizure type, epilepsy having different aspects at different ages. Thus, small children under the age of 1 year may present seizures in the form of *infantile spasms*, semiologically considered as generalized seizures that occur in clusters, related to sleep, usually at waking, but also at falling asleep. After their onset, children will have psychomotor arrest or regression, usually losing some motor and cognitive acquisitions. The interictal awake EEG shows a characteristic pattern – chaotic, high- to extremely high–voltage rhythms, intricated with epileptiform discharges called hypsarrhythmia. These three features define West syndrome, a specific infancy related generalized epileptic syndrome, with variable etiology from idiopathic (genetic cause) to symptomatic (cortical brain lesions). The evolution is generally unfavorable, these seizures being resistant to classic AED's, while some patients have favorable response to corticotherapy.

Children with NF1 have an increased prevalence of West syndrome, 0.76%, higher than the general population (0.05%) (5). The EEG shows a specific pattern for West syndrome, namely hypsarrhythmia and brain MRI of these children usually shows only typical subcortical NBO's of NF1. The evolution of these children is favorable in 50% of cases, with seizure control under ACTH therapy. In 3 patients with West syndrome associated to NF1 there have been found other chromosomal abnormalities, but no genotype-phenotype correlation was possible. In our study, none of the patients had infantile spasms.

Febrile seizures may be another type of seizures associated with NF1, simple febrile seizures (onset between 1-5 years, high fever, such as generalized tonic-clonic seizures in children with positive family history for epilepsy) being the most often described association. (3). From the described series, Maria is the girl with NF1 who presented complex febrile convulsions, but with a favorable evolution, normal psychomotor development, and without repeating the paroxysmal events and not requiring antiepileptic treatment.

As with any epilepsy secondary to structural brain damage, we expect and find that in NF1 there have been described more often focal than generalized seizures (8). In our study, Valentin and Alexandru presented focal seizures, but only the first one with a favorable outcome and complete therapeutical response.

Iulia has NF1 and a generalized epilepsy, Lennox-Gastaut syndrome, presenting in addition to focal seizures, myoclonic or generalized tonic seizures, with a specific EEG pattern. Iulia's epilepsy evolution was that specific to Lennox-Gastaut syndrome, with a poor outcome, persisting seizures with no therapeutical response and psychomotor delayed evolution.

Epilepsy is a common symptom of neurocutaneous syndromes, along with other phacomatoses as tuberous sclerosis or Sturge-Weber syndrome (leptomeningeal angiomatosis), but the last ones associate cortical brain lesions that are incriminated in abnormal neuronal networks that have seizures as symptoms. In NF1 cortical lesions are generally not associated and therefore the question that arises is what is causing these cortical paroxysmal discharges. Two possible hypotheses was considered as possible: if there is a direct cause-effect between brain lesions and cortical hyperexcitability or if there is an association linked to genetic factors involved both in determinism of NF1 and epilepsy.

It is known that NF1 is a neurocutaneous syndrome with brain structural changes such as NBO's seen on MRI and there have been studies in litera-

ture that tried to make a correlation between their type, number and epileptic seizures. They showed that the number of NBO's was higher in children with epilepsy and NF1 than those without associated seizures, but this difference was not statistically significant and a direct correlation between NBO's and seizures onset was not found (9).

Also regarding macroscopic brain structural abnormalities, it was raised the suspicion that it could be an association between the seizures and the tumors as gliomas or malignant tumors (but these appear in a low incidence), malformations as cortical dysplasia (very rare in NF1) or vascular (no cases described with NF1, vascular abnormalities and epilepsy).

Due to the fact that a direct link between macroscopically demonstrable lesions and epileptic seizures could not be proved, it was considered that maybe there are microscopic cortical abnormalities that could not be revealed by structural conventional imaging. Thus, pathological studies have shown that the NBO's may associate microscopic lesions such as neuronal heterotopias and spongiotic changes (10), changes that may have 'epileptogenic properties'.

On the other hand, PET studies have shown areas with metabolic abnormalities other than NBO's described by cerebral MRI, which could be considered as having a possible epileptogenic role (9).

The MRI performed to the children in our study showed specific lesions only for those 2 who had unfavorable evolution, without being able to make a direct link between NBO's and the seizures onset. This association between clinical evolution and the presence of NBO's, seen in only 2 patients, needs to be quantified on a larger lot of patients with NF1 and specific brain lesions before considering as a poor prognostic predictive factor.

Another theory that supports the link between NF1 and epilepsy is the genetic. NF1 is a genetic neurocutaneous syndrome secondary to a chromosome 17q abnormality that leads to increased expression of neurofibromin. This protein exists physiologically in large amounts in embryonic brain, being involved in the differentiation of neurotransmitters and synaptic neural networks formation. Thus, it is suspected that pathological expression of neurofibromin in patients with NF1 may also result in aberrant neural networks with low epileptogenic threshold (11,12).

Taking into consideration the favorable specific response of vigabatrin in tuberous sclerosis related epilepsy, it was investigated a possible favorable association between some antiepileptic drugs and NF1 associated epilepsy (5), but no specific treatment was discovered, the recommendations being that the treament should be addressed to the specific epileptic syndrome associated, disregarding etiology in this case (8). 50% of patients respond to antiepileptic treatment, percentage also reported in our study.

Evolution of epileptic seizures in NF1 is specific to each associated epileptic syndrome, with remission in some cases and pharmacoresistance in others, usually the type of seizures at onset will remain in general the same throughout evolution. The psychomotor development of these children is frequently associated with learning and attention deficit disorders, especially if they have NBO's in the thalamus (9).

CONCLUSIONS

From our study, although done on a small number of patients who associate NF1 and epilepsy, it appears that there is a higher prevalence than in the general population, similar to that described in the literature, and that the association with NBO's may have poor prognosis related to resistance to classical AED's.

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It is important to be mention that we have analyzed the clinical features of these types of epilepsy related to neurofibromatosis, which is genetic disease through a research project of genetic epilepsy (Rare Epileptic Syndromes – Euroepinomics).

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